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Influence of Nicotine (i.v.) and Tobacco Smoking on Blood Flow in Human Skin and Skeletal Muscle

SUMMARY

Several methods were used to measure the response of the peripheral circulation to nicotine administered intravenously. Nicotine decreases blood flow in skin and increases it transiently in resting skeletal muscle.

METHODS

Three methods have been used in this study for measurement of blood flow in muscle.

1. Impedance plethysmograph with venous occlusion
2. Volume plethysmograph with venous occlusion
3. Hensel thermoelectric needle

At the start of the study it was felt that the only method which could be assumed to be quantitatively valid was the volume plethysmograph, but that published records of Nyboer showing parallel results from the impedance and volume plethysmograph offered a reasonable expectancy that it would be possible to determine a factor permitting conversion of results of the impedance plethysmograph into volume flows. Given a valid conversion factor the experiments could proceed using only the impedance plethysmograph and the Hensel needle, the use of the needle permitting a distinction as to whether changes in the cross section blood flows as determined by plethysmograph were due to changes in blood flow in muscle or skin. Furthermore, the impedance plethysmograph, unlike the volume plethysmograph, would allow measurements by both devices in the same calf. Unfortunately the impedance plethysmograph proved unsatisfactory.

1. The impedance plethysmograph consisted of a stable 100 kilocycle oscillator, a transformer coupled impedance bridge on AC amplifier with phase demodulator and finally an Edin DC amplifier driving one channel of a Photron direct writing oscillograph. Tow aluminum wire electrodes wet with electrode paste and secured with Elastoplast adhesive bandage encircled the ends of the limb segment being studied and conducted a fixed 100 kilocycle current to the tissue.

Between these electrodes another pair of similar electrodes picked up the voltage resulting from the passage of the current and returned this voltage to the bridge.

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In conjunction with the Edin amplifier, the stability and sensitivity of the instrument were reasonably adequate as a physical device.

As the work proceeded, it became apparent that the impedance and the volume plethysmographs, when applied to the same limb segment, were not measuring the same physiological variable. The two records following individual venous occlusions were often closely equivalent, but when the segmental blood flow had changed by various means such as Priscoline, Adrenaline, heat etc. the ratio between the two results occasionally changed in unexpected ways and sometimes in opposite directions. Furthermore, there was an unexpected difference in the nature of the artefact which usually followed occlusion. Finally there were frequent sudden changes in impedance which were not accompanied by changes in the volume record.

As a result of these discrepancies between the impedance and the volume methods it was not considered that any reliable interpretation could be placed on the impedance results, hence it was not used in later studies of drug action.

2. The volume plethysmograph finally adopted consisted of an acrylic tube 4 inches long and 5-3/4 inches inside diameter with flanged ends and a connection for 1/2 inch tubing. Rubber sleeves tailored to fit casts of a variety of legs and terminated by rubber flanges were fitted over the cuff and secured to the plethysmograph by clamping the rubber flanges of the sleeves between the flanges on the ends of the plethysmograph and lucite rings, pressure being maintained by spring clamps reaching between rings on opposite ends of the plethysmograph. In general this device is quickly applied, and, as it does not depend upon a seal between instrument and skin, there has been little trouble with leakage.

Displaced air volume, actually a change which is partially volume and partially pressure but always proportional to volume displacement, was measured by Lilly Technitrol capacitance manometer with special extremely low pressure head having a diaphragm of 4 inch diameter made of 2 mill. brass. Calibrating volumes were inserted into the system by means of a 5 ml. hypodermic syringe.

A pneumatic cuff was applied just above the knee and produced venous occlusion by inflation from a reservoir yielding a cuff pressure of approximately 55 mm.

To eliminate return flow from the foot a second pneumatic cuff was applied aroung the ankle and was inflated to 180 to 190 mm.Hg just before the start of each series of venous occlusions. The use of this distal cuff limited the length of a series of blood flow measurements. The short time interval required between successive occlusions precluded release and reinflation of this distal cuff between venous occlusions.

3. The Hensel thermoelectric needle consists of a 19 gauge steel hypodermic needle enclosing two iron-constantan thermocouples, series opposing to measure temperature differences, and an electric heater. One of the thermocouples is at the tip of the needle, the other 1 cm. away from the tip. The heater heats the tip of the needle.

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As used by Hensel, the needle is heated by alternating current from the line via transformer and rheostat, and the differential temperature is measured by galvanometer or photoelectric galvanometer recorder.

As used in this study the differential temperature was measured by a Brown strip chart recorder with 10°C scale and heating was by a 1000 cycle current with a very stable oscillator, the use of the higher frequency being necessitated by the sensitivity of the Brown recorder to 60 cycle current. When used in various calibrating media such as water, glycerine, vaseline etc. the results checked with those using the 60 cycle heating current, hence the two systems are equivalent, with the Brown recorder giving the higher sensitivity.

The Hensel needle derives immediately from a similar but less satisfactory device by Grayson but ultimately from related devices from three other laboratories, Gibbs', Rhein's and Schmidt's. In refinement of design it appears to leave little room for improvement and its stability is remarkable.

The sensitivity to blood flow is due to the movement of blood carrying away heat from the heated thermocouple at the tip of the needle. Increases of blood flow result in a decreased temperature differential between the heated and unheated thermocouples.

The operation of the Hensel needle depends upon introducing it into a satisfactory location, this being defined as: a location, where, with the heat off, three minute arterial occlusions, and the subsequent reactive hyperemia, produce little or no change in the temperature difference between the two thermocouples; but where, with the heat on, a fairly good increase in differential temperature follows arterial occlusion and a still larger decrease in differential temperature follows release of a three minute arterial occlusion.

In our studies excellent results were obtained when a satisfactory site in the muscle was located but we had much more difficulty in locating satisfactory sites than Hensel's publications would imply, with the result that in over half of the experiments no results were obtained from the Hensel needle.

The final design of the experiment used in studies of the effects of nicotine on blood flow in human muscle consisted of the following procedure:

a. The left calf was iontophoresed with adrenaline 1:1000 at a pH of 3.5 and a current of 30 milliamperes producing a profound and longlasting vasoconstriction of the affected skin area well beyond that included under the plethysmograph.

b. The volume plethysmograph was applied to the left calf, a proximal pneumatic cuff was applied above the knee to produce venous occlusions and a cuff was placed around the ankle to prevent blood flow in the foot from affecting measurements.

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c. Following intracutaneous infiltration of procaine, the Hensel needle was inserted into the right gastrocnemius muscle, with heating current off. When the differential temperature became steady a proximal pneumatic cuff was inflated to 180 mm. for 3 minutes, then released. If no appreciable change of the differential temperature occurred the distal thermocouple was heated 4-5° above the proximal thermocouple and the occlusion and release was repeated. If a satisfactory response (0.3° or better) was not obtained on release of the occlusion, the needle was moved slightly and the occlusions repeated. When a satisfactory site for the tip of the needle was found the needle was ready to make measurements of blood flow for an indefinite period with no further attention.

d. The distal cuff on the left ankle was then inflated and a series of venous occlusions was started and while they were continued 6 micrograms of adrenaline was injected over 15 seconds via an intravenous drip of 5% glucose. The needle site was considered satisfactory, and was used for collection of data on nicotine, by the Hensel technique, only after a typical transient response to adrenaline was obtained. After a waiting period of 10 to 15 minutes baseline flows by both methods were recorded, and nicotine was injected I.V.; the dose in these experiments varied between 0.6 to 4 milligrams and the duration of administration was either 1 or 4 minutes. While continuous readings were obtained with the needle, venous occlusions were made repeatedly for a period of about 10 minutes, and then the ankle cuff was deflated. Plethysmographic measurements were discontinued (needle readings continued) for 10 to 15 minutes. Then the ankle cuff was reinflated and a final series of measurements by both methods was made.

In most of the experiments with 1 minute injections the use of the Hensel needle was attempted. Successful sites were obtained in nearly half the instances, and there was good correlation between these results and those by plethysmograph. In most of the experiments with 4 minute injections the Hensel needle was not used.

65 subjects were used, including those in preliminary trials.

RESULTS

1. 41 Cases (58 injections): The injection of 6 micrograms of adrenaline during 15 seconds invariably resulted in a large but very transient increase in the blood flow in the calf muscle.

2. 16 Cases: The injection of 2 milligrams of nicotine in smokers over a period of 1 minute produced a significant increase in the mean muscle flow over the period between 1 and 3 minutes after start of injection.

3. Due to spontaneous variations in blood flow and the limited number of measurements possible during the response to nicotine, the results were not significant in every individual subject but were significant for the group (i.e. young, healthy male smokers).

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4. 3 Cases: The results for non-smokers are not clearly significant because of the small numbers of non-smokers subjected to smoking and the high frequency of nausea; however, the few individuals tested showed a greater vascular response than did the smokers.

5. In the two instances in which 2 milligrams of nicotine were injected more slowly, over a period of 4 minutes, in smokers there was no appreciable change in blood flow to muscle.

6. 18 Cases: The injection of 3 milligrams of nicotine, to smokers, over 4 minutes produced a large increase in muscle blood flow. In one case a like response was produced with 4 milligrams.

7. In no case did the injection of nicotine produce a decrease in the blood flow to the muscle. The usual result is a transient increase followed by an unstable period with intermittent small increases. The statistical significance of the instability has not yet been determined.

8. There was no significant long term effect on the muscle blood flow following nicotine injection. The trend appears to be slightly upward but it would take many more cases to establish significance.

9. In the small number of cases where reliable measurements were obtainable by the needle as well as the plethysmograph, good substantiation was obtained of the conclusion that the increase in flow occurred in muscle rather than in the adrenaline iontophoresed skin around the muscle. This conclusion was further strongly substantiated by thermal observations on digital blood flow, previously made, and by inclusion of a digital plethysmograph in some of the experiments herein reported which invariably showed a decrease of skin flow following the nicotine injection.

10. The injection of nicotine produced marked decrease in digital blood flow (plethysmograph) and in distal volume pulse with onset preceding the increase in muscle blood flow. These cutaneous vascular effects were more sustained than were the muscular.

SUMMARY OF CONCLUSIONS

Nicotine given intravenously causes a transient increase in blood flow in resting skeletal muscle.

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